Attorney's Docket No.: 10274-034001 / A061

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Mundy et al.
Serial No. : 09/805,840
Filed : March 13, 2001
Title : METHODS OF TREATING MULTIPLE MYELOMA AND MYELOMA-INDUCED BONE RESORPTION USING INTEGRIN ANTAGONISTS

Art Unit : 1644
Examiner : Maher M. Haddad, Ph.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132 OF DR. BLAKE PEPINSKY

I, Blake Pepinsky, a citizen of U.S.A. residing in Arligton, MA, hereby declare as follows:

1. I am Director of Protein Chemistry at Biogen Idec Inc. I received my doctorate in Biochemistry from Cornell University, where I also completed postdoctoral training. I have over 20 years experience in the field of antibody therapeutics and small molecule therapeutics. I have published over 120 scientific articles, including 24 articles specifically on integrin studies. I serve or have served on the editorial boards of over a dozen different scientific journals.

2. I have reviewed and understand the contents of the present patent application.

3. I have been advised and understand that the Examiner has rejected claims 1, 2, 4, 5, 9, 31-32 and 34-39, which are directed to methods of treating multiple myeloma with an anti-α4 integrin antibody, as unpatentable in view of a combination of references: U.S. Patent No. 6,495,525 to Lee et al. (Lee); U.S. Patent No. 5,932,214; and Kamata et al. The Examiner argues that, at the time of priority (September 14, 1998) one of ordinary skill in the art would have been

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motivated to substitute the anti-α4 antibodies taught by U.S. Patent No. 5,932,214 and Kamata for the small molecule oMePUPA-V taught by Lee, to treat multiple myeloma.

4. In fact, a practitioner of ordinary skill in this field would not have believed that oMePUPA-V would be interchangeable with anti-α4 integrin antibodies to treat multiple myeloma. It would have been unpredictable that an antibody against α4 integrins would have the same effect as any anti-VLA-4 (α4/β1 integrin) small molecule, much less oMePUPA-V. Antibodies are completely different than small molecules. In the first place, antibodies as a class of agents are vastly different in size than small molecule drugs such as oMePUPA-V. Due to its small size, a small molecule drug is typically directed to a "pocket" or specific docking site on the target molecule, where by that very nature it may act as either an agonist or an antagonist. In contrast, antibodies are large molecules and, while they may bind to a particular epitope on a target, they effectively cover a large surface area and thereby act to block a biological pathway though stearic hindrance, as opposed to binding a specific active site or pocket. In many cases, some target pockets are simply not accessible to antibodies. This is the case in the present situation. That is, oMePUPA-V binds at the ligand binding site and therefore may act as an agonist. In contrast, none of the existing anti-α integrin antibodies bind directly at the ligand binding site. For this reason alone, a skilled practitioner would not have believed oMePUPA-V to be interchangeable with an anti-α4 integrin antibody.

5. Moreover, unlike oMePUPA-V, an antibody-based therapeutic would be expected to implicate aspects of the immune response in its effect. The Fc domain of antibodies of particular isotypes can bind to immune effector cells that express Fc receptors on their surface, allowing antibodies to recruit immune effector cells and complement factors to their site. The binding of some Fc receptors by antibodies provides signals that activate and recruit immune and inflammatory cells, whereas engagement of other Fc receptors can send inhibitory signals that downregulate immunity. For example, FcRIII is an activation receptor that acts to activate macrophages, natural killer cells and mast cells. However, FcRIIB is an inhibitory receptor expressed on macrophages (but not natural killer cells) that co-ligates to FcRIII activation receptors, leading to inhibition of FcRIII signaling. The possible implication of such immune

mechanisms with an anti-α4 integrin antibody could have been predicted to result in a completely different effect in vivo than that of oMePUPA-V. Thus, a skilled practitioner would not have reasonably predicted that an anti-α4 integrin antibody would have the same effect as oMePUPA-V in vivo. Such antibody-specific mechanisms are an important reason why an antibody and a small molecule would not be considered interchangeable.

6. In addition, an anti-α4 integrin antibody would not have been expected to have the same in vivo effect as oMePUPA-V in particular because anti-α4 integrin antibodies have a different specificity than oMePUPA-V. Lee teaches that oMePUPA-V is highly specific for VLA-4 (having α4/β1 subunits) but does not act on α4/β7 integrin (see Lee, column 7, lines 39-42; and column 25, lines 33-34). In contrast, the α4 integrin antibodies recited in the claims can bind both α4/β1 and α4/β7, implicating an additional integrin pathway. The broader specificity of an anti-α4 integrin, compared to oMePUPA-V, would have made it unpredictable that an anti-α4 antibody would have the same effect as oMePUPA-V in vivo at all, much less have the same applicability across such a broad range of disorders and particularly against any one particular listed disorder, such as multiple myeloma.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Blake Papinsky
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1/29/04
Date

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